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Endocrine therapy in epithelial ovarian cancer

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ABSTRACT

Introduction: The estrogen receptor (ER) is expressed at high levels in many epithelial ovarian cancers (EOC) and represents a potential target for endocrine therapy. Both anti-estrogens and aromatase inhibitors have been evaluated in phase II clinical trials.

Areas covered: We present an overview of the phase II and phase III trials of anti-estrogens (tamoxifen and fulvestrant) and aromatase inhibitors (letrozole, anastrozole and exemestane) undertaken in epithelial ovarian cancer identified through a Pubmed search. We describe predictive biomarkers that are being investigated to identify responsive cancers.

Expert commentary: The efficacy of endocrine therapy in epithelial ovarian cancer is likely to be confined to histological subtypes with the highest ER expression while low grade serous ovarian cancer appears to be one subgroup with good sensitivity to these agents. The low toxicity profile of these agents is favourable although their use is unlicensed and the optimal setting undefined. Prospective clinical trials of endocrine agents in the early relapse and maintenance settings are urgently required to establish their definitive role in the management of epithelial ovarian cancer

KEYWORDS: ovarian cancer, estrogen receptor, tamoxifen, fulvestrant, letrozole, anastrozole

1. Introduction

Ovarian cancer is the most lethal gynaecological malignancy in the Western World [1]. In 2012, there were estimated to be 239,000 new cases diagnosed worldwide with around 152,000 deaths from the disease [2]. The lifetime risk of developing ovarian cancer is currently 1 in 75 and the chance of dying from the disease is approximately 1 in 100.

Epithelial ovarian carcinoma (EOC) is a heterogeneous disease comprising of five main histologically defined subtypes: high grade serous (HGS) (70%), low grade serous (LGS) (<5%), endometrioid (EC) (10%), clear cell (10%) and mucinous ovarian carcinoma (3%) [3]. Each sub-type is molecularly diverse with distinct origins, biology and clinical behaviours [4]. HGS largely originates in the fimbriated end of the fallopian tube, is characterised by almost ubiquitous TP53 mutations and inactivation of genes involved in homologous recombination DNA repair such as *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* or aberrations in genes that impact on cell cycle control such as *CCNE1*, *RB1* and *NF1* [5 – 7]. Clear cell and endometrioid ovarian cancer both often arise within the context of endometriosis; they are associated with mutation of *ARID1A*, *PIK3CA* and *PTEN* [8, 9]. Low grade serous ovarian cancer is associated with activation of the MAPK pathway through mutations of *BRAF*, *KRAS* or *NRAS* and high levels of estrogen and progesterone receptor expression [10 – 12]. Mucinous ovarian cancer is a diminishingly rare entity with most believed to be metastatic lesions from non-ovarian sites of origin. Those felt to truly arise from the ovary are characterised by overexpression of *KRAS* and amplification of *HER2* [13, 14].

The vast majority of HGS and LGS ovarian cancer patients will present with advanced disease at diagnosis. Endometrioid, clear cell and mucinous ovarian cancers are more likely to present with early stage disease. All histological subtypes are managed similarly with maximal cyto-reductive surgery and platinum and taxane-based combination chemotherapy forming the current standard of care. This is despite the clinical, pathological and genomic diversity displayed by each sub-type [15]. Response rates are high but unfortunately most patients presenting with advanced disease will relapse. Relapsed ovarian cancer may be suspected on the basis of a rising CA125. No survival advantage has been demonstrated for initiating chemotherapy in the context of a rising CA125 in an otherwise asymptomatic patient [16]. The use of anti-estrogen therapy in this setting to prolong the time to next chemotherapy is possible given its low toxicity and ease of administration. However, its use is unlicensed and the evidence confined to a limited number of small phase II studies. There is currently no standard of care regarding the use of endocrine therapy in EOC, largely due to the lack of large randomised studies being performed in this setting. The degree of estrogen receptor (ER) expression appears to correlate with the degree of endocrine sensitivity [17]. However, the majority

of these studies included patients with both ER positive and ER negative relapsed EOCs. Different methods and thresholds of determining ER positivity were used. They also included patients of all histological subtypes who were heavily pre-treated with chemotherapy. The results of these trials are likely to have been diluted by these factors. As such, the use of endocrine therapy in EOC is inconsistent worldwide.

1.1 Estrogen sensitivity of ovarian cancer

Several lines of evidence - both preclinical and clinical - support the view that many ovarian cancers are growth regulated by estrogen. ER is expressed in 61-79% of EOCs [18]. The Ovarian Tissue Analysis Consortium Study found HGS, EC, and LGS ovarian cancers to have the highest levels of strong ER positivity (defined as $\geq 50\%$ tumor nuclear staining) of 60%, 60% and 71% respectively [19]. This is in contrast to clear cell (14%) and mucinous (16%) carcinomas. The endocrine sensitivity of individual histotypes is largely unknown. One notable exception to this is in low grade serous ovarian cancer in which Gershenson et al [20, 21] have performed retrospective analyses of endocrine sensitivity in both the relapsed disease and first line maintenance settings (described in more detail below).

Cultured ovarian cancer cells with high levels of ER expression can be growth-stimulated by estrogen *in vitro* while anti-estrogens can be growth inhibitory both *in vitro* [22, 23] and *in vivo* [24]. Both of the major isoforms of ER, ER-alpha ($ER\alpha$) and ER-beta ($ER\beta$), are expressed in ovarian cancers and there has been much speculation as to their roles. $ER\alpha$ is the isoform strongly associated with endocrine-sensitivity in breast cancer and is the isoform most clearly linked to estrogen's activity in ovarian cancer [25]. Multiple studies have shown that $ER\alpha$ -positive ovarian cancer cells are responsive to 17β -estradiol *in vitro* [22, 25]. The *in vitro* data was supported by *in vivo* studies of human ovarian cancer xenografts implanted and grown in immunodeficient mice [23]. Anti-estrogens including tamoxifen and fulvestrant were demonstrated to have efficacy against $ER\alpha$ -positive xenografts [24]. Conversely, there is no effect of estrogen on $ER\alpha$ -negative cell lines [25].

The prognostic value of $ER\alpha$ appears to differ with different histological subtypes. The Ovarian Tumor Analysis Consortium study (2933 patients) was the largest study to examine the prognostic role of hormone receptors in EOCs [11]. $ER\alpha$ and progesterone (PgR) expression was associated with improved survival in EC ovarian cancers but only PR expression was prognostic in HGS ovarian cancers. There was no demonstrable association between ER, PgR and survival in LGS, clear cell and mucinous carcinomas although there were low numbers of patients with these histological subtypes included in this study [19, 26]. The role of $ER\beta$ is more complex [27]. Expressed at high levels in normal ovarian surface epithelial cells, its expression is reduced in ovarian cancers

and even further in metastatic deposits [28-31]. Insertion of ER β into ovarian cancer cells resulted in reduced proliferation [30]. The gene is localized on Chromosome 14q and this region is frequently deleted in ovarian cancer [30]. These observations would be consistent with a tumor suppressor role for this receptor isoform [30].

Further evidence suggesting that estrogen may influence the incidence of ovarian cancer has been obtained from studies monitoring the use of hormone replacement therapy (HRT). Meta-analyses of large datasets including the Million Women study have shown that the risk of ovarian cancer is increased 1.28-fold in women using HRT compared to never users [32]. Estrogen-only formulations appeared to carry a higher risk than estrogen / progesterone combinations and both the dose and duration are associated with enhanced risk [32].

Finally, there have been a large number of Phase II clinical trials with anti-estrogens and aromatase inhibitors conducted which have demonstrated significant activity (low response rates but with significant disease stabilisation) in ovarian cancers and these are discussed below.

1.2 1980-2000: Tamoxifen trials

The earliest clinical studies evaluating anti-estrogens in ovarian cancer used tamoxifen and this agent continues to be used. Tamoxifen is a selective estrogen receptor modulator (SERM) that binds to ER α and competes with estrogen, thereby acting as an ER antagonist. In 1981, Myers et al described responses in three ovarian cancer patients [33] and this was followed by multiple Phase II clinical trials being conducted between 1981 and 2000 with most of these listed in Table 1 [34-53]. The response rates in these trials varied from 0 – 56% while the disease stabilisation rate varies between 0 and 83%. Overall the mean response rate is of the order of 10-15% and the disease stabilisation rate of the order of 30-40%. The daily doses used varied between 20 and 40mg tamoxifen with some studies using a higher loading dose (Table 1).

Despite the large number of trials that have been undertaken, there still remain many questions surrounding the efficacy of tamoxifen in this disease that are unanswered. Many of these questions have been discussed in analyses of these datasets and these have sought to identify the strengths and weaknesses of the data.

Williams and colleagues reviewed and analysed a large number of small tamoxifen trials that totalled 623 patients [54]. In the trials considered, a total of 60 of 623 patients (9.6%) responded to tamoxifen while 131 of 411 patients (31.9%) demonstrated disease stabilisation. The authors argued that while tamoxifen appears to have modest activity in the treatment of recurrent advanced

ovarian cancer, there were no randomized studies comparing tamoxifen with supportive care only hence it was difficult to judge the true level of activity of the drug [54]. The phase II trials were designed as single arm studies to assess whether tamoxifen could induce responses in patients but did not address survival, symptom control and quality of life issues [54]. The size of the individual trials made it difficult to identify differences in response rates between histological subtypes and the predictive value of ER expression to endocrine sensitivity of these tumors was not addressed [54].

Perez-Gracia and Carrasco [55] also analysed the tamoxifen clinical trial literature and covered a similar but not identical set of clinical trials [55]. Their review of 648 treated patients revealed an overall response rate of 13% (95% C.I. 10.4 – 15.6) with a 4% complete response rate and 9% partial response rate. Furthermore, 38% of patients had stable disease. They pointed out that compared to breast cancer where tamoxifen is used as first line treatment, many ovarian cancer patients were heavily pretreated and resistant to chemotherapy by the time they were treated with tamoxifen. When they selected trials in which at least 50% of patients had not received more than one prior treatment (240 patients), the overall response rate doubled to 25.8% with an 8.8% complete response rate; conversely for the heavily pretreated patients (314 patients) the overall response rate was only 4.1% [55]. They also emphasised that patients were not selected on the basis of ER status (as in breast cancer) and again highlighted the uncertainty around its value for predicting tamoxifen response.

Tamoxifen has also been used in asymptomatic patients with recurrent small-volume disease after primary or secondary chemotherapy as a management option [56]. Fifty-six patients who experienced recurrence of malignancy were treated and of these, 42% and 19% of patients remained on tamoxifen for > 6 and >12 months respectively before re-initiation of cytotoxic chemotherapy. It was concluded that in the absence of data from randomized controlled trials, tamoxifen is a reasonable management option in this situation [56]. It could not be established however whether the delay obtained was as a result of tamoxifen efficacy or simply reflected more indolent disease [56].

A randomized phase III trial of tamoxifen versus thalidomide (GOG#198) in EOC, fallopian tube or primary peritoneal cancer was reported in 2010 by Hurteau et al [57]. This trial sought to compare survival and toxicities of the two drugs in “biochemically recurrent” disease. Progressively rising CA125 is frequently the first sign of recurrent disease and precedes the development of clinical symptoms by a median of 3 months [58]. Within this trial, tamoxifen was used as the “reference” arm but proved more effective than thalidomide with only 3% of tamoxifen-treated patients experiencing grade 3 or 4 toxicities with improved overall survival and reduced risk of death [57].

The tamoxifen arm produced superior progression free and overall survival than thalidomide [57]. The trial however did not contain a no-treatment or placebo group, nevertheless these results are encouraging.

Tamoxifen has been studied in combination with Gefitinib (Iressa) which targets the epidermal growth factor receptor [59]. Of 56 patients treated, no patients demonstrated an objective response but 16 patients had stable disease [59]. In combination with goserelin, a gonadotropin-releasing hormone (GnRH) agonist, tamoxifen produced an overall response rate (clinical benefit rate) of 50% [60]. This included one complete response (3.8%), two partial responses (7.7%) and 10 patients with stable disease (38.5%) [60].

1.3 Fulvestrant trial

A single phase II trial of Fulvestrant (Faslodex), an anti-estrogen that acts as an ER α down-regulator, was reported in 2009 [61]. Twenty-six patients with ER-positive disease were treated with fulvestrant (500mg IM on Day 1, then 250mg IM on Days 15 and 29, then every 28 days thereafter). All patients had been heavily pretreated and had received a median of 5 chemotherapeutic regimens prior to fulvestrant treatment. Disease response was assessed by measurement of CA125 levels and by CT scans. Using modified Rustin criteria for CA125 response, there was 1 complete response (4%) (normalisation of CA125 level), 1 partial response (4%) (> 50% decrease in initially elevated CA125 level) and 9 patients with stable disease (35%). Using RECIST criteria, 13 patients (50%) demonstrated stable disease. The study concluded that while response rates were low, disease stabilisation was common [61].

1.4 2002 onwards: Aromatase inhibitor trials

Since 2002, a number of Phase II clinical trials have evaluated selected aromatase inhibitors (AIs) against ovarian cancer (Table 2) [17, 62 – 69]. These agents act by inhibiting the conversion of androgen to estrogen through aromatization and in breast cancer have become the preferred option in treating endocrine-sensitive disease. Both letrozole and anastrozole have been evaluated in multiple trials although letrozole has been studied in a much larger number of patients (Table 2) while only a single report has described the use of exemestane [69]. Letrozole was administered orally at 2.5mg/day, anastrozole at 1mg/day orally and exemestane at 25mg/day orally in these studies.

The first trial of letrozole, reported in 2002, evaluated letrozole (2.5 mg p.o.) in 60 patients of whom 50 were evaluable [17]. While there were no complete or partial responses as judged by CT scan, 10 patients had disease stabilisation for > 12 weeks. CA125 responses were evaluable in 54 patients. A marker response (> 50% decrease) was seen in 5 patients, while the marker remained stable in another 14 patients. This study demonstrated that the degree of ER α expression (specifically ER immunoscore \geq 150) predicted for CA125 responses and disease stabilisation (discussed in detail below).

Based on the results of this trial, a second study was undertaken in patients with an ER immunoscore \geq 150 [63]. Of 42 patients evaluable for CA125 response, 7 (17%) had a CA125 response (i.e. 50% decrease in initially elevated CA125 level) and 11 (26%) had CA125 stabilisation following 6 months on treatment. Of 33 patients evaluable for radiological response (RECIST criteria), 3 (9%) had a partial response and 14 (42%) had stable disease [63]. The CA125 response rate increased from 9% in patients unselected for ER α expression to 17% in patients with an ER immunoscore \geq 150 [63]. Similarly, the CA125 stabilisation rate increased from 25% to 36% in these two groups of patients. These two trials provide good evidence that the degree of ER α expression correlates with the degree of endocrine sensitivity. This is discussed further below.

Comparable clinical benefit results were demonstrated in a study reported by Papadimitriou in 2004 [62]. Twenty-seven patients were treated and 21 had measurable disease that was evaluable. A 15% RECIST response rate (1 complete response, 2 partial responses) was obtained while the CA125 response rate (i.e. 50% decrease in initially elevated CA125 level) was 15% (4 of 27 patients) and CA125 stabilisation was observed in another 5 patients (18%) [62].

There have been other trials of letrozole in relapsed EOC which have included both ER positive and negative patients and have used different ER scoring methods and treatment thresholds. These are summarised in table 2.

Ramirez et al in 2008 evaluated letrozole in recurrent platinum- and taxane-resistant high grade cancer of the ovary or peritoneum [65]. One patient (3%) had a partial response while 7 patients (23%) had stable disease.

Two further smaller studies have been reported [64, 66]. In a study of 13 patients with recurrent advanced low malignant potential or LGS ovarian tumors reported by Kavanagh et al, 5 patients (38%) demonstrated disease stabilisation although no patient had an objective response [64]. For

CA125 response, 2 of 15 patients demonstrated a complete serological response while another 2 demonstrated a partial serological CA125 response. Marker stabilisation was observed in a further 5 (38%) of patients. In a study of 14 chemotherapy resistant patients with recurrent disease reported by Tchekmedyian et al, 10 patients had sustained stability or evidence of clinical improvement while on treatment with an average duration of 12 months [66].

Two trials have to date been reported for anastrozole [67, 68]. The first reported by Del Carmen used anastrozole at 1mg/day in 53 patients [67]. One partial response was noted but 42% of patients demonstrated stable disease [67]. The second study was a combination study of anastrozole and the EGF receptor inhibitor gefitinib. The disease stabilisation rate in this study was 61% and a single response was observed [68].

A Phase II trial of exemestane in 24 refractory ovarian cancer patients was reported in 2006 [69]. While no patient demonstrated an objective response, 36% (8 of 22) patients had stable disease for > 14 weeks.

1.5 Aromatase inhibitors in recurrent low-grade serous ovarian cancer

In addition to the above studies, there have been analyses in certain subgroups such as LGS ovarian cancers. Gershenson reported on a retrospective series of 64 patients with LGS ovarian cancers who were treated with 89 hormonal regimens at the MD Anderson hospital. 50 of these patients had tissue available for ER and PR expression analysis. Hormone receptor positivity was defined as nuclear staining $\geq 1\%$ and all 50 patients were ER positive and 50% of patients were PR positive by this criterion. This is perhaps the only study to examine endocrine sensitivity in a single histological sub-type as well as allow a more direct comparison between letrozole, anastrozole and tamoxifen in EOC [20]. In total, 6 patients had a complete response (6.7%) and 2 patients had a partial response (2.2%) giving an overall response rate of 9%. 61% of the patient regimens had a progression free survival of 6 months or greater. The effect of indolent tumor biology of LGS may have potentially influenced this. Of 33 patients treated with letrozole, 4 demonstrated a complete response, 2 a partial response and 17 disease stabilisation. For 21 patients treated with anastrozole, 1 demonstrated a complete response and 14 disease stabilisation. For 17 patients treated with tamoxifen, 1 showed a complete response and 11 demonstrated disease stabilisation [20]. These results suggest that the efficacy between these three agents is very similar.

A recent retrospective analysis has compared hormonal maintenance therapy with surveillance in LGS ovarian cancer after completion of primary therapy (primary cyto-reductive

surgery and adjuvant chemotherapy) [21]. The majority of patients were treated with letrozole (57%), and others with tamoxifen (32%), anastrozole (5%) and leuprolide acetate (5%). Median progression free survival for hormonal therapy was 52 months compared to 29.9 months for matched surveillance patients ($p = 0.001$). Patients on hormonal therapy had a significantly reduced rate of recurrence compared to those on surveillance (Hazard ratio = 0.21; $p < 0.001$). The investigators concluded that women with stage II to IV LGS ovarian cancers who received hormonal maintenance therapy had a significantly improved progression free survival compared to those on surveillance alone [21].

A case report described two patients with recurrent low malignant potential serous ovarian tumors who were progressing on chemotherapy were subsequently treated with anastrozole and demonstrated complete remissions. The patients have been followed up for 11 and 7 years respectively without relapse [70]. These data support the potential value of AIs in LGS ovarian cancers.

1.6 Predictive biomarkers

There have been a number of predictive biomarkers of endocrine sensitivity identified, but perhaps the most prominent of them all is ER α expression.

The early phase II tamoxifen trials did not select patients for ER α expression. Attempts were made to investigate ER α as a potential biomarker of response but the results were disappointing. Many of these trials were very small with too few responders or had insufficient numbers of tumors being measured for ER expression to have adequate power to evaluate an association. However, it is of interest that in the largest study of 105 patients, 8 of 9 (89%) patients who demonstrated a complete response had a level of ER α > 12 fmol/mg protein whereas only 48 of 82 (59%) with stable or progressive disease had this level of expression [36]. Although this difference was not statistically significant, it is in line with a requirement for a higher level of ER α expression being associated with tamoxifen response.

More detailed biomarker-directed studies have focussed on two of the letrozole clinical trials [17, 63] and the fulvestrant trial [61]. Antitumor response has been linked to expression of selected proteins [17, 63, 71 - 73]. Foremost of the markers that has emerged is ER α expression itself.

The first letrozole trial described an association between increased ER α expression and increased probability of response [17]. The response criteria were based on CA125 response or stabilisation as per Rustin's criteria and CT response as per UICC criteria. ER α expression was measured by immunohistochemistry and an immunoscore was calculated for an individual tumor. This varied between 0 and 300 for an individual tumor and was a composite of staining intensity and percentage positivity [17]. The probability of response increased steadily in tumors with ER α expression between 0 and 300 ($p = 0.0087$). Patients with an ER immunoscore greater than or equal to 150 and PgR score of greater than 70 had a 64% disease stabilisation rate compared to 3% of patients with scores lower than this. This resulted in a follow-up study wherein patients were selected for trial entry based on an ER α expression immunoscore of 150 or higher [63]. Within this extension trial, it was demonstrated that within the 3 cohorts with immunoscores of 150-199, 200-249 and 250-300, CA125 response rates increased from 0%, to 12% and 33% respectively (alongside a high rate of CA125 stabilisation in each group) [63]. In the group with the highest levels of ER α expression (immunoscore = 250-300), 17% of patients demonstrated a partial response and 67% had disease stabilisation as assessed by RECIST criteria.

A more recent study [71] has analysed fixed tissue from the ovarian cancers treated in the Phase II fulvestrant trial [61]. Within this trial, approximately half of the 26 patients treated derived clinical benefit at 90 days as assessed by either modified Rustin CA125 criteria (43%) or RECIST criteria (50%) [61]. Clinical benefit (CB) was assessed as the sum of complete and partial responses and disease stabilisation as opposed to progressive disease [61]. The clinical benefit group had a statistically higher mean ER α immunoscore than the progressive disease group consistent with a higher level of ER α expression being associated with improved outcome [71].

These results however require further validation as several other studies have not observed an association with ER α expression [62, 74]. While ER α expression was evaluated in most of the AI trials, it was generally to confirm that a minimum level of expression was present hence expression of > 1% cells positive as indicated by immunohistochemistry was regarded as indicative of ER-positivity. The studies using more detailed immunoscore suggest that higher levels of ER α expression than the minimum are more likely to be associated with response [17, 63, 71]. The study by Papadimitriou [62] did evaluate high, intermediate low and negative levels of ER but could not find an association with response, however the investigators did note that the 3 responders were all ER-positive [62]. A retrospective study aiming to determine the progression-free interval for patients with platinum-resistant ovarian cancer on anti-estrogen therapy investigated the correlation of progression free interval with tumor ER expression status [74]. ER positivity was measured using the

Allred scoring and a cut-off score was not defined. 99 patients were evaluated, 77 received tamoxifen, and only 22 received an aromatase inhibitor. 66 patients were evaluable for ER status; 44 were positive and 19 were negative. The median progression free interval for anti-estrogen therapy was 4 months (range 1-49 months) in ER-positive patients which was comparable to that obtained with standard cytotoxic therapies. No association was found between ER expression and the progression free interval. The low toxicity profile, ease of oral administration and low cost of anti-estrogen therapy led the investigators to argue that anti-estrogen therapy should be considered in all patients with platinum-resistant ovarian cancer irrespective of ER expression level [74].

The rationale for the selection of ER α as a biomarker was based on experience of anti-estrogens in breast cancer and its clear value in that context. As such, several other predictive markers useful in breast cancer were also investigated. Higher PGR expression was observed to associate with RECIST disease stabilisation as opposed to progression in the initial letrozole trial [17]. The epidermal growth factor receptor (HER family) proteins, EGFR (HER1) and erbB2 (HER2) were both shown to be associated with changes in CA125 expression levels [17].

A series of other markers that have shown some promise were initially identified predominantly from a microarray study that sought to identify estrogen-regulated gene expression changes in ER α -positive ovarian cancer [25]. Within that study, estrogen-regulated gene expression was demonstrated to be mediated by ER α rather than ER β . A set of candidate biomarkers were evaluated in primary tumor sections obtained from patients treated in the first letrozole study [17]. One interesting family of proteins that emerged was the insulin-like growth factor binding proteins (IGFBPs) [72]. Three family members (IGFBP3, IGFBP4 and IGFBP5) were shown to be estrogen-regulated *in vitro* with IGFBP3 and IGFBP5 being down-regulated by estrogen while IGFBP4 is up-regulated [72]. These effects were reversed by tamoxifen [72]. In ovarian cancer samples obtained during the phase II trial, IGFBP3 and IGFBP5 were lower, and IGFBP4 expression higher, in primary cancers that were responsive to letrozole relative to those that progressed on treatment, and this would be consistent with an estrogen-drive in responsive tumors as predicted by the *in vitro* experiment [72]. Another family of estrogen-regulated proteins is the trefoil factor family and both TFF1 (pS2) and TFF3 are up-regulated by estrogen in ER α -positive ovarian cancer cells *in vitro* [73]. Consistent with an estrogen-drive in the letrozole sensitive cancer group, the tumors that demonstrated clinical benefit had a statistically higher level of expression of both these markers [73]. Similarly, up-regulated in the letrozole-responsive group were TNF receptor-associated protein 1 (TRAP1), topoisomerase II alpha (TOP2A) and ubiquitin-conjugating enzyme E2C (UBE2C) [73]. Three molecules identified as being down-regulated in tumors that are responsive, again in line with the *in vitro* studies, are plasminogen activator urokinase (PLAU), beta-IG-H3 (BIGH3) and vimentin

(VIM) [73]. Several of these markers (HER2, TFF1, IGFBP5 and VIM) were validated in the 2nd Letrozole study [63]. Two of these biomarkers (TFF1 and VIM) correlated with an improved progression-free survival from material obtained in the fulvestrant study [71]. These studies now require further validation to confirm the possible value of these biomarkers.

1.7 Ongoing trials

Several clinical trials investigating anti-estrogen agent use in ovarian cancer are underway at present. A trial of anastrozole for hormone receptor positive gynaecological cancers (PARAGON) has recently closed to recruitment [75]. This is a Phase II study designed to include 350 women with ER and/or PR positive gynecological cancers including patients with EOC, endometrial cancer or sarcomas and sex cord stromal tumors of the ovary.

A phase II/III trial of trametinib (a MEK inhibitor) is currently underway in recurrent or progressive LGS and is being compared with letrozole or tamoxifen citrate (both p.o. days 1-28) among other comparator arms (NCT02101788) [76]. This trial will provide further information on these anti-estrogens in LGS.

In another trial, Regorafenib (a multi-kinase inhibitor) is undergoing comparison with tamoxifen in platinum-sensitive ovarian cancer (NCT02584465) [77].

The combination of anastrozole and the mTOR inhibitor everolimus has been investigated in 10 ovarian cancer patients as part of a larger study evaluating breast, ovarian and endometrial cancers with this combination [78]. This is based on the rationale that PI3K/AKT/mTOR pathway activation can diminish the effects of hormonal therapy, hence the use of the mTOR inhibitor [79]. Two of the 10 ovarian cancer patients treated demonstrated stable disease after treatment with this combination [78].

2. Expert Commentary

The data summarised thus far suggest that there is a role for endocrine therapy in EOC. However, the optimal setting and biologically relevant patient population have not been defined. There has been no phase III randomised controlled trial of endocrine therapy versus placebo in relapsed EOC,

nor has the role of endocrine therapy as maintenance or adjuvant therapy ever been prospectively explored. Its effect on progression free survival or overall survival is unknown. Apart from extrapolated data from breast cancer, there is no quality of life data for patients on these therapies. As such, its use worldwide is sporadic and inconsistent. Some centres use endocrine therapy as first line therapy in the asymptomatic Ca125 relapsed setting, whilst others only use it in later settings when patients have exhausted most chemo-therapeutic options. Also, the use of ER for patient selection is highly variable.

The available clinical studies consistently demonstrate a modest (10-15%) objective response rate, with a further (approximately 30%) disease stabilisation rate with the use of endocrine therapy. The activity level of the aromatase inhibitors appears similar to that for tamoxifen and there is currently no demonstrable superiority of one agent over the other. Some clinicians would choose aromatase inhibitors over tamoxifen on the basis that use of the latter carries more of a thrombotic risk which is important in patients who have a high incidence of pelvic disease.

Although multiple endocrine trials have been carried out, most consist of relatively small numbers of patients who were unselected for ER positivity and heavily pre-treated which may be masking the true potential of anti-estrogen therapy. One analysis of the use of tamoxifen in trials in which at least 50% of patients had received not more than one prior treatment indicated an objective response rate of 25.8% with an 8.8% complete response rate (240 patients) in contrast to trials of heavily pretreated patients (314 patients) where the objective response rate was only 4.1% [55]. Although the best settings for use of these therapies have not been defined, it is likely that early use of endocrine therapy in the course of relapsed ER positive EOC is likely to improve response rates and prolong the time to next therapy.

The data supports the degree of ER α expression as the best predictor of endocrine sensitivity. Other markers may eventually prove to have value although larger confirmatory studies are required. The histological subtypes with the highest ER expression are HGS, LGS and EC ovarian carcinomas. These subtypes are likely to derive the greatest benefit from endocrine therapy although their individual endocrine sensitivity is under-investigated.

LGS ovarian cancer has emerged as a biologically distinct entity compared to HGS ovarian cancer. It has been shown to be relatively chemotherapy resistant (response rates 4%) and have a far more indolent course with better prognosis [79]. It is perhaps the only histological subtype in which response rates to endocrine therapy have been independently studied [20]. In light of these data, oncologists are increasingly questioning whether hormonal therapy may be a more suitable

first line therapy than chemotherapy for recurrent disease. This has been emphasised by a recent ASCO presentation by Gershenson *et al* [21] which demonstrated the potential role of adjuvant or maintenance hormonal therapy following primary therapy for LGS ovarian cancer. Although this was a retrospective study with its associated bias, there is little doubt that this study warrants further prospective evaluation in a placebo-controlled randomised phase III study which is stratified for histological sub-type.

Endometrioid ovarian cancer is a poorly understood histological sub-type in part due to evolving pathological definitions which re-classifies most high grade ECs as HGS ovarian cancers [80, 81]. Its natural history, treatment responses and clinical outcomes are not well defined. From the published data, it tends to present at an earlier stage and overall has a better prognosis compared to HGS ovarian cancer [82]. High grade ECs bear close histological resemblance to HGS ovarian cancers and global gene expression studies have shown these two subtypes to cluster together suggesting similar underlying biology. In contrast, low grade ECs closely resemble endometrioid uterine carcinomas and also share common molecular alterations such as *CTNNB1*, *PIK3CA*, *PTEN* mutations and microsatellite instability, but with differing frequencies [83]. It is likely that low grade EC is a highly endocrine sensitive tumour akin to endometrioid uterine carcinoma [84]. Again the role of endocrine therapy as treatment and potential adjuvant therapy needs to be considered separately in this sub-group of patients at the same time considering that most low grade ECs are unlikely to relapse. Prior to this however, EC ovarian cancers need to be formally defined at the clinical, pathological and genomic level.

HGS ovarian cancers form the majority of EOCs with the most patients presenting with advanced disease and having a poor prognosis. Although endocrine sensitivity has never been explored solely in this histotype, HGS represented the majority of the patient population in most of the endocrine studies performed to date and the data obtained from these studies are likely to reflect this fact.

3. Five-year view

Hopefully, the future role of endocrine therapy in EOC will be similar to that of breast cancer whereby it is used in the adjuvant (first line), maintenance and relapsed settings. However, in order to reach this point a number of uncertainties require to be resolved. Firstly, the extent of endocrine sensitivity in the separate histological subtypes will require to be determined. Secondly, the optimal setting for such treatment (whether it be adjuvant, maintenance or primary therapy for relapse) will

require to be established for each of these histological subtypes. Thirdly, we need to identify the extent to which sensitivity can be predicted by biomarkers. Fourthly, for patient subgroups which are shown in future trials to particularly benefit from endocrine therapy we need to consider the order that endocrine agents are administered and whether there is a case for sequential administration in the adjuvant setting (very much akin to the breast cancer situation). Finally, in patients who have clear evidence of endocrine sensitivity, mechanisms of resistance require to be explored. This would pave the way for the development of newer endocrine agents or indeed support the need to perform clinical trials of combination therapy of endocrine agents and targeted novel agents akin to the licensed use of the aromatase inhibitor, letrozole, and CDK4/CDK6 inhibitor, palbociclib, in metastatic breast cancer [85]. Some of these goals will take more than five years to achieve but if we can develop clinical trials now to systematically address them then there is good reason to believe that the outcome for ovarian cancer patients can be improved.

Key Issues

- Many ovarian cancers express high levels of ER.
- Higher levels of ER α expression are associated with improved response rates to endocrine therapy; other biomarkers are in development.
- ER α expression is prognostic in certain histological subtypes but not in others.
- Multiple phase II studies of endocrine therapy have been conducted with most containing patients who were heavily pre-treated and unselected for ER.
- ER positivity has been measured and defined in different ways across the studies.
- The overall response rates to tamoxifen, fulvestrant, letrozole and anastrozole are low in the order of 10-15% however approximately 30% of patients demonstrate disease stabilisation.
- Endocrine therapy is used in relapsed EOC although its use is unlicensed and the optimal setting is undefined.
- LGS ovarian cancer has demonstrated good endocrine sensitivity in retrospective studies.
- Prospective clinical trials of endocrine agents in the early relapse and maintenance settings are required to define their role in the management of each histological sub-type of EOC.
- Resistance mechanisms need to be explored in endocrine sensitive tumors so that newer agents and combination therapies can be developed.

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Table 1. Phase II trials of tamoxifen in recurrent epithelial ovarian cancer

Investigator	Daily dose (mg)	No.	ORR	CR	PR	SD	PD	Ref
Schwartz et al.	20	13	8 %	0	1	4	8	[34]
Weiner et al.	40 then 20	31	10%	1	2	6	22	[35]
Hatch et al.	40	105	17%	10	8	40	47	[36]
Shirey et al.	20-40	23	0%	0	0	19	4	[37]
Slevin et al.	40	22	0%	0	0	1	21	[38]
Osborne et al.	100 then 40	51	2%	0	1	0	50	[39]
Hamerlynck et al.	40	36	6%	0	2	7	27	[40]
Landoni et al.	40	55	0%	0	0	19	36	[41]
Pagel et al.	20	21	38%	1	7	12	1	[42]
Campbell et al.	20	13	8%	1	0	NS	NS	[43]
Rowland et al.	20	9	0%	0	0	NS	NS	[44]
Jakobsen et al.	30	17	0%	0	0	NS	NS	[45]
Ahlgren et al.	40 then 20	29	17%	2	3	18	6	[46]
Jager et al.	30	33	0%	0	0	2	31	[47]
Van Der Velden et al.	40	30	7%	2	0	10	18	[48]
Gennatas et al.	40	50	56%	2	26	NS	NS	[49]
Trope et al.	30 - 40	66	6%	2	2	51	11	[50]
Rolski et al.	40	47	6%	1	2	22	22	[51]
Quinn et al.	20	40	23%	5	4	12	19	[52]
Karagol et al.	40	29	10%	1	2	6	20	[53]

No. = number of patients ; ORR = Objective response rate (CR + PR / No.) ; CR = Complete response ; PR = Partial response ; SD = Stable disease ; PD = Progressive disease ; NS = Not stated

Table 2. Phase II trials of aromatase inhibitors in recurrent epithelial ovarian cancer

No.	ORR	CR	PR	SD	PD	ER measurements	Previous lines of CT	Investigator (Ref)
Letrozole								
54	9%	0	5	14	30	IS (97% ER+)	1(50%), ≥2(50%)	Bowman et al [17]
27	15%	1	3	5	18	IHC (73% ER+)	1(59%), ≥2(41%)	Papadimitriou [62]
42	17%	0	7	11	24	IS (IS > 150)	1(52%), ≥2(46%)	Smyth [63]
13	31%	2	2	5	4	IHC (Not stated)	Not stated	Kavanagh [64]
33	3%	0	1	7	23	IHC (All ER+)	1 (6%), ≥2(94%)	Ramirez [65]
14	36%	5	0	5	4	13/13 ER+*	Mean = 2.8	Tchekmedyan [66]
Anastrozole								
53	2%	0	1	22	30	IHC (71% ER+)	1(28%), ≥ 2(72%)	Del Carmen[67]
23	4%	1	0	14	8	IHC (All ER+)	Not stated	Krasner[68]
Exemestane								
22	0%	0	0	8	14	IHC (41% ER+))	1(32%), 2(68%)	Verma[69]

No. = number of patients ; ORR = Objective response rate (CR + PR / No.) ; CR = Complete response ; PR = Partial response ; SD = Stable disease ; PD = Progressive disease ; IHC = Immunohistochemistry (ER+ defined as ≥ 1% positive except for Ref[48] where ER ≥ 5% positive); IS = Immunoscore (ER varies between 0 and 300; ER+ defined as IS ≥ 1) ; Previous lines of chemotherapy (CT)= Number of lines (% of patients). Letrozole was administered at 2.5mg/day, Anastrozole at 1mg/day and Exemestane at 25mg/day; *ER measurement method not stated